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(71) Applicant *(for GB only)*: **PFIZER LIMITED** [GB/GB]; Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(71) Applicant *(for all designated States except GB, US)*: **PFIZER INC.** [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BASFORD, Patricia, Ann** [GB/GB]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). **HODGSON, Paul, Blaise** [GB/GB]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(74) Agents: **WOOD, David, J.** et al.; Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

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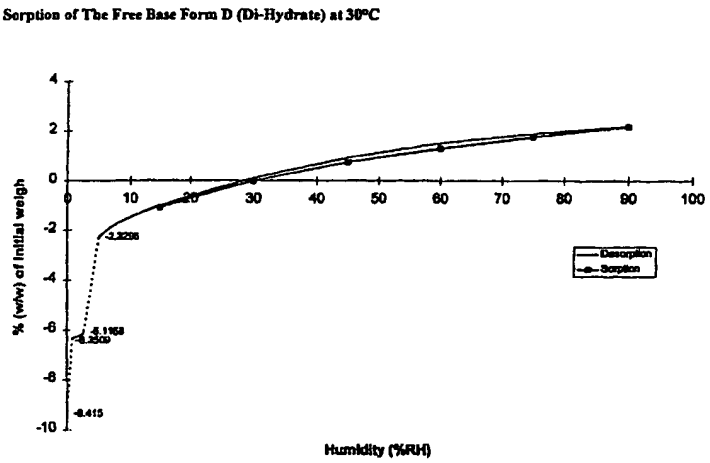
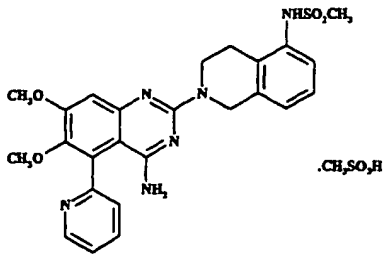
(54) Title: 4-AMINO-6,7-DIMETHOXY-2-(5-METHANESULFONAMIDO-1,2,3,4-TETRAHYDROISOQUINOL-2-YL)-5-(2-PYRIDYL)QUINAZOLINE MESYLAT AND POLYMORPHS





(1)

(57) Abstract: The present invention provides 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline mesylate of the formula (1) together with processes for preparing, and compositions containing it. The invention also relates to substantially pure anhydrous crystalline polymorphic forms of the free base. The compounds are particularly useful in the treatment of benign prostatic hyperplasia.

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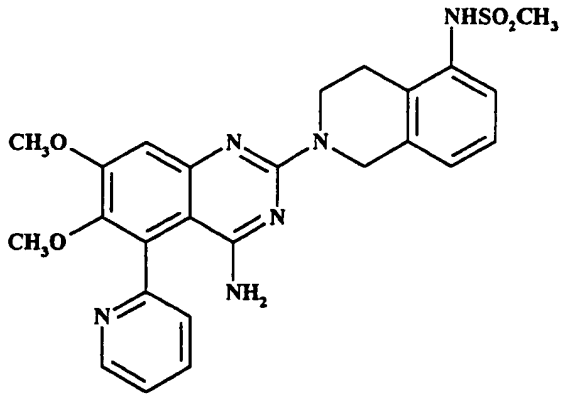
4-AMINO-6,7-DIMETHOXY-2-(5-METHANESULFONAMIDO-1,2,3,4-TETRAHYDROISOQUINOL-2-YL)-5-(2-PYRIDYL)QUINAZOLINE MESYLAT AND POLYMORPHS

The present invention relates to a novel salt useful in therapy. More specifically the present invention relates to 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline mesylate, to processes for its preparation, to its uses, and to compositions containing it. The present invention also relates to novel non-hydrated polymorphs of the free base.

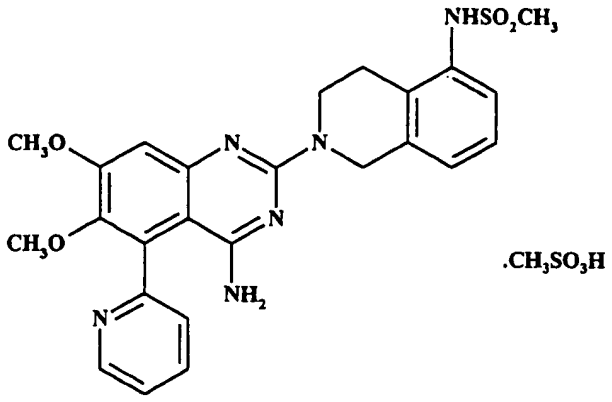
4-Amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline has the formula



and is disclosed in WO 98/30560 (see Example 19) as being useful in the treatment of benign prostatic hyperplasia. The application refers in general terms to pharmaceutically acceptable salts and mentions the hydrochloride, hydrobromide and phosphate salts.

Unfortunately, 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline displays some disadvantageous physical properties. It is now known to occur in a number of different forms. In some cases, its aqueous solubility is rather low and it is difficult to prepare reproducibly in the same form, sometimes being obtained in a hydrated form. In addition, it has been found that some forms of the free base are rather hygroscopic. These properties are disadvantageous for the development of a drug substance because, in particular, a consistent grade of material must be reproducibly manufactured in order to satisfy regulatory requirements.

There is now provided the mesylate salt of 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline having the formula



This substance has a number of unexpected advantages over the free base and it has surprisingly been found to have a unique combination of properties which make it ideal for development as a drug substance.

Those skilled in the art will appreciate that "mesylate" is an alternative term for "methanesulfonate".

The mesylate salt has a high melting point, and is a crystalline solid which does not display any hydrated or solvated forms. It is isomorphic, i.e. it exists in a single polymorphic form, and exhibits good stability over a wide range of conditions, e.g. high light intensity. It has acceptable solubility and dissolution characteristics, and can be economically prepared and processed to provide suitable solid dosage forms of the drug. Its hygroscopicity is substantially lower than the free base (tested as its 198°C melting point polymorph) over a wide range of relative humidity. The mesylate salt is monomorphic and does not form hydrates; both of these features represent advantageous properties of the mesylate salt in particular.

Tables 1 to 3 below indicate the physical properties of 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline mesylate and some free base forms.

Table 1

Physical properties of the mesylate salt

Form	Melting Point (°C)	Crystallinity	Hygroscopicity % (w/w) at 90% RH
Mesylate Salt	279	Crystalline	1.1

Table 2

Solubility of the mesylate salt and free base forms (micrograms/ml)

Solvent	Free base (mpt 198°C)	Hydrated form of free base	Mesylate salt
Water at 22°C	420	12	880
0.9% sodium chloride at 22 °C	36	4	120

Table 3

Hygroscopity of the mesylate salt and free base forms

Form	Moisture sorption (% w/w) at 30°C and 45% RH
Free base (mpt 198°C)	1.39
Hydrated form of free base	11.24
Mesylate salt (mpt 279°C)	0.56

The present invention also includes the substantially pure anhydrous crystalline forms of 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline (the free base). These anhydrous polymorphs are designated Form A, Form B, Form C, and Form E in Table 4 below. Form D, which is presented for comparison, is the hydrated form and exists as a dihydrate.

The term "substantially pure" used above means that a sample of the relevant anhydrous crystalline form contains more than 90% of a single polymorphic form, preferably more than 99% of a single polymorphic form.

Table 4

Polymorphic forms of the free base

Form	Melting point (°C)	Crystallinity	Hygroscopity % (w/w) at 90% RH
Form A	198	crystalline	2.2
Form B	218	crystalline	0.27
Form C	147	crystalline	-
Form E	229	crystalline	0.045
Form D	None	crystalline	12.8

On dehydration, the hydrated form (Form D) becomes amorphous.

The anhydrous polymorphic forms of the invention are also significantly less hygroscopic than the hydrated free base form. Of these, Forms B and E are preferred on account of their high melting points and low hygroscopicity. Form E is most preferred.

It is now believed that the solid form of 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline produced originally following the procedure of WO 98/30560 (see Example 19) was a mixture of Forms B and E, probably in the ratio 1:1 (based on a differential scanning calorimetry experiment showing sharp endotherms at 220 and 227°C). Following the creation of the most stable Form E in pure form, it is likely that this form will be produced predominantly in the future when repeating the above preparation of 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline.

Also included within the scope of the present invention are radiolabelled derivatives, other isotopic forms and tautomers of 4-amino-6,7-dimethoxy-2-(5-

methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline in the form of the anhydrous free base or the mesylate salt.

4-Amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline in one of its free base polymorphic forms or as the mesylate salt possesses pharmacological activity in animals. It may be used in the treatment of a number of conditions including hypertension, myocardial infarction, male erectile dysfunction, hyperlipidaemia, cardiac arrhythmia and benign prostatic hyperplasia. The latter condition is of greatest interest. Thus, according to another aspect of the invention, there is provided a method of treatment of benign prostatic hyperplasia which comprises administering a therapeutically effective amount of 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline in the form of the anhydrous free base or the mesylate salt to a patient suffering from such a disorder.

According to a further aspect of the invention, there is provided 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)-quinazoline in the form of the anhydrous free base or the mesylate salt for use as a pharmaceutical; and for use in the treatment of benign prostatic hyperplasia.

According to a further aspect of the invention, there is provided the use of 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)-quinazoline in the form of the anhydrous free base or the mesylate salt in the manufacture of a medicament for the treatment of benign prostatic hyperplasia.

4-Amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline in the form of the anhydrous free base or the mesylate salt can be administered alone but will generally be administered in admixture with a suitable pharmaceutical excipient, diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

Hence, according to a further aspect of the invention, there is provided a pharmaceutical formulation including 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline in the form of the anhydrous free base or the mesylate salt in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier. The formulation will preferably contain less than 50% by weight of 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline in a free base polymorphic form or as the mesylate salt.

For example, 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline in the form of the anhydrous free base or the mesylate salt can be administered orally, buccally or sublingually in the form of tablets, capsules, ovules, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for immediate-, delayed- or controlled-release applications. Oral administration is of particular interest. 4-Amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline in the form of the anhydrous free base or the mesylate salt may also be administered *via* intracavernosal injection.

Such tablets may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate and glycine, disintegrants such as starch (preferably corn, potato or tapioca starch), sodium starch glycollate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included.

Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline in the form of the anhydrous free base or the mesylate salt may be combined with various sweetening or flavouring agents, colouring matter or dyes, with

emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

4-Amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline in the form of the anhydrous free base or the mesylate salt can also be administered parenterally, for example, intravenously, intra-arterially, intraperitoneally, intrathecally, intraventricularly, intrasternally, intracranially, intramuscularly or subcutaneously, or may be administered by infusion techniques. It is best used in the form of a sterile aqueous solution which may contain other substances; for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art.

For oral and parenteral administration to human patients, the daily dosage level of 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline in the form of the anhydrous free base or the mesylate salt will usually be from about 0.01 to 10mg/kg (in single or divided doses) and preferably about 0.01 to 0.5mg/kg, administered from 1 to 4 times a day.

Thus tablets or capsules of 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline in the form of the anhydrous free base or the mesylate salt may contain from about 0.1mg to 500mg of active compound for administration singly or two or more at a time, as appropriate. The physician in any event will determine the actual dosage which will be most suitable for any individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited and such are within the scope of this invention.

4-Amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline in the form of the anhydrous free base or the mesylate salt can also be administered intranasally or by inhalation and is conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray or nebuliser with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134A [trade mark]) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA [trade mark]), carbon dioxide or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container, pump, spray or nebuliser may contain a solution or suspension of the active compound, e.g. using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline in the form of the anhydrous free base or the mesylate salt and a suitable powder base such as lactose or starch.

Aerosol or dry powder formulations are preferably arranged so that each metered dose or "puff" contains from 20μg to 4mg of 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline in the form of the anhydrous free base or the mesylate salt for delivery to the patient. The overall daily dose with an aerosol will be in the range of from 20μg to 20mg which may be administered in a single dose or, more usually, in divided doses throughout the day.

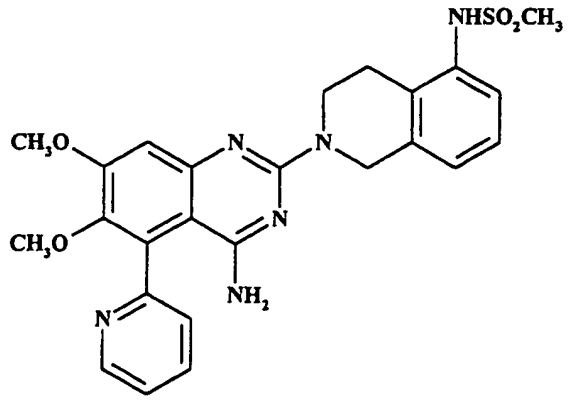
Alternatively, 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline in the form of the anhydrous free base or the mesylate salt can be administered in the form of a suppository or pessary, or may be applied topically in the form of a lotion, solution, cream, ointment or dusting powder. 4-Amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline in the form of the anhydrous free base or the mesylate salt may

also be transdermally administered, for example, by the use of a skin patch. It may also be administered by the ocular route, particularly for treatment of the eye.

For ophthalmic use, it can be formulated as micronised suspensions in isotonic, pH adjusted, sterile saline, or, preferably, as solutions in isotonic, pH adjusted, sterile saline, optionally in combination with a preservative such as a benzylalkonium chloride. Alternatively, it may be formulated in an ointment such as petrolatum.

For application topically to the skin, 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline in the form of the anhydrous free base or the mesylate salt can be formulated as a suitable ointment containing the active compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, it can be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

The invention further provides a process for the preparation of 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl) quinazoline mesylate, as defined above, which comprises the addition of methanesulphonic acid to a suspension or solution of 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline of the formula



in a suitable solvent, and collection of the precipitated solid.

Preferred features of the process include:

(a) the solution of 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline is maintained at a temperature above room temperature before the addition of the methanesulphonic acid; and

(b) the solvent used is a mixture of butanone and water, for example a 10:1 by volume mixture of butanone and water.

The process may be defined more particularly as a process comprising the steps of:

(a) heating a suspension of 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline in butanone/water to reflux;

(b) adding butanone/water until a solution is achieved;

(c) cooling the solution;

(d) adding methanesulfonic acid; and

(e) collecting the resulting solid by filtration.

In the above processes, it is preferred that the 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline is present as Form E, although some of the desired product should result regardless of the starting form.

The formulations of the invention may also contain a human 5-α reductase inhibitory compound [see International Patent Application WO-A-95/28397], or 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline in the form of the anhydrous free base or the mesylate salt could be presented in a pharmaceutical pack also containing a human 5-α reductase inhibitory compound as a combined preparation for simultaneous, separate or sequential use.

References herein to treatment include curative, palliative and prophylactic treatment.

The four anhydrous polymorphs of the free base which have been isolated have been designated Forms A, B, C and E. These polymorphic forms were characterised by powder X-ray diffraction (PXRD), together with the mesylate salt.

The powder X-ray diffraction patterns were determined using a SIEMENS D5000 powder X-ray diffractometer fitted with an automatic sample changer, a theta-theta goniometer, automatic beam divergence slits, a secondary monochromator and a scintillation counter. The samples were prepared for analysis by packing the powder into 12mm diameter, 0.25mm deep cavities that had been cut into silicon wafer specimen mounts. Each specimen was rotated whilst being irradiated with copper K-alpha$_1$ X-rays (wavelength = 1.5406 Ångstroms) with the X-ray tube operated at 40kV/40mA. The analyses were performed with the goniometer running in step-scan mode set for a 5 second count per 0.02° step over a two theta range of 2° to 55°. The peak intensities are summarised in Table 5. In Table 5, "Angle 2-Theta" is related to the interplanar spacing of the crystal, and the intensity is given as a percentage of the greatest peak (I/I_1). The individual polymorphic forms and the mesylate salt may be characterised by reference to the peak intensities of greater than 50%, and more preferably by the peaks having intensities greater than 20%.

Table 5
Peak listings for Forms A, B, C and E, and the mesylate salt

Form A

Angle 2-Theta °	Intensity %	Angle 2-Theta °	Intensity %	Angle 2-Theta °	Intensity %	Angle 2-Theta °	Intensity %
6.002	21.1	15.669	4.7	23.282	40.8	30.469	15.3
8.893	22.9	17.040	30.0	23.494	37.3	31.498	17.4
9.401	25.1	17.888	33.4	23.884	92.4	32.257	8.8
9.654	8.5	18.111	16.7	24.298	42.7	33.063	11.6
11.105	33.4	18.872	51.9	24.554	18.7	33.797	14.1
12.000	100.0	19.287	18.9	24.602	19.6	34.889	17.1
12.071	50.2	19.336	16.0	25.674	30.1	35.158	21.2
13.060	25.1	19.714	7.2	26.087	13.8	35.610	12.5
13.373	10.3	20.126	6.5	26.600	19.1	36.226	13.8
13.458	11.6	20.951	15.3	27.036	11.8	36.634	12.4
13.620	10.0	21.021	12.9	27.641	24.4	38.335	16.0
13.708	15.5	21.302	15.4	28.888	18.3	40.198	17.2
13.790	10.8	21.378	19.9	29.136	14.6	40.820	13.7

14.418	10.9	21.925	57.5	29.915	9.4	41.279	15.7
15.075	4.3	22.346	94.6	30.197	19.4	43.943	20.5
15.320	6.1	22.821	22.7	30.282	25.8		

Form B

Angle 2-Theta °	Intensity %	Angle 2-Theta °	Intensity %	Angle 2-Theta °	Intensity %	Angle 2-Theta °	Intensity %
6.943	1.4	19.559	8.4	26.512	36.5	34.214	9.3
9.004	37.5	19.867	11.1	26.758	30.5	34.382	12.2
9.725	41.2	19.964	6.1	26.918	20.7	34.602	7.7
10.526	40.7	20.407	62.2	26.989	25.4	35.235	10.4
11.315	3.4	20.919	31.2	27.302	7.2	35.449	13.0
11.986	2.1	21.101	17.3	27.800	17.4	36.193	6.8
13.011	2.2	21.712	14.4	27.871	11.6	36.668	8.1
13.493	30.2	22.551	72.7	28.945	9.5	37.331	12.6
13.897	74.4	22.769	20.2	29.164	14.4	37.727	8.4
14.306	3.3	22.843	13.9	30.027	7.5	38.318	5.4
15.569	25.2	22.926	15.3	30.284	10.2	38.977	11.3
15.883	48.3	23.418	100.0	31.179	19.9	39.646	15.8
16.740	5.9	23.904	24.9	31.443	10.2	40.165	7.8
17.122	30.0	23.997	24.5	31.629	8.7	40.911	5.3
17.407	12.3	25.049	21.4	32.121	8.1	42.235	10.8
17.603	5.7	25.209	32.4	32.318	7.9	42.761	9.8
18.094	4.1	25.462	17.0	32.845	12.2	44.287	7.2
18.727	62.9	25.700	8.4	33.023	14.8	44.775	9.5
19.176	10.0	26.205	12.9	34.045	9.5		

Form C

Angle 2-Theta°	Intensity %	Angle 2-Theta°	Intensity %	Angle 2-Theta°	Intensity %	Angle 2-Theta°	Intensity %
5.510	4.2	17.488	24.7	25.257	52.6	31.939	28.9
6.143	4.4	18.601	76.6	25.885	19.4	32.689	14.9
7.860	63.2	18.964	32.9	26.283	22.0	33.228	13.6
8.141	13.2	19.230	16.8	26.634	28.5	33.880	16.4
9.774	8.0	19.727	51.4	27.085	17.6	34.867	15.1
10.290	12.0	20.121	29.0	27.309	20.8	35.627	16.9
11.076	6.9	20.440	10.1	27.574	28.7	36.765	14.7
11.262	6.3	20.859	14.5	27.904	19.1	37.551	19.7
12.133	24.3	21.261	19.4	28.165	14.3	38.576	20.2
12.510	7.5	21.730	100.0	28.891	19.3	39.190	23.3
12.860	14.2	22.310	39.0	29.226	15.1	40.302	16.8
13.690	37.3	22.830	72.0	29.792	30.7	40.824	16.8
14.446	8.5	23.102	27.7	30.101	19.7	41.643	15.1
15.008	35.4	23.598	75.9	30.287	15.7	42.238	16.6
15.794	32.6	23.884	24.7	30.604	17.0	42.971	19.4
16.274	27.9	24.479	50.5	30.771	16.9	44.714	16.4
16.781	14.6	24.777	21.2	30.995	11.5		
16.940	10.7	25.093	59.3	31.590	22.4		

Form E

Angle 2-Theta °	Intensity %	Angle 2-Theta °	Intensity %	Angle 2-Theta °	Intensity %	Angle 2-Theta °	Intensity %
8.416	6.3	18.028	12.3	23.852	100.0	32.434	14.8
8.506	3.9	18.387	6.4	24.075	18.0	32.760	25.6
9.675	23.0	18.787	17.0	24.192	18.9	34.083	8.6
11.994	15.7	19.315	38.5	24.696	10.7	34.462	7.8
12.393	13.7	19.358	42.2	25.280	28.2	34.927	5.6
13.116	8.2	19.444	31.1	25.765	11.1	35.552	7.1
13.952	16.4	19.778	26.6	26.061	12.1	36.390	7.2
14.064	17.2	20.056	6.9	26.746	8.5	36.954	6.3
15.978	5.8	20.398	3.5	27.269	10.6	37.993	7.1
16.096	3.7	21.522	7.5	28.860	13.0	39.826	4.7
16.218	3.6	21.770	7.7	29.534	5.3	40.699	8.4
16.914	30.8	22.479	8.2	29.642	7.9	42.316	7.0
17.042	13.4	22.974	5.0	31.094	4.3	43.410	7.0
17.596	10.3	23.509	7.0	31.652	4.0		

Mesylate salt

Angle 2-Theta °	Intensity %	Angle 2-Theta °	Intensity %	Angle 2-Theta °	Intensity %	Angle 2-Theta °	Intensity %
7.392	22.9	19.297	57.9	26.55	16.8	34.607	6.7
7.56	12.1	20.265	51	26.818	15.3	35.031	8.4
9.129	18.4	20.494	7.3	27.012	30.3	35.834	9.6
10.179	11	20.772	13.8	27.675	15.9	36.125	9.2
11.871	17.8	21.018	15.1	28.673	22.3	36.418	9.3
12.343	7.6	21.414	40	28.904	16.3	37.675	10
13.057	18.6	22.136	24	29.305	24.6	38.92	6.3
14.5	11.1	22.804	16.7	29.627	9.1	40.614	5.9
14.733	22.6	22.934	32.8	29.93	9.3	41.061	8.8
14.813	40.1	23.283	8.7	30.327	14.9	41.65	13.3
15.162	5.4	23.842	49.4	30.663	16.8	42.03	10.4
17.155	10.6	24.5	14.4	30.999	16.7	42.65	10.1
17.694	31	24.795	100	31.297	12.8	42.878	8.9
18.358	6.5	25.452	7.6	31.841	6	44.003	7.7
18.602	6.1	26.201	5.2	32.844	16.5	44.817	9.3
18.964	40.5						

Differential scanning calorimetry (DSC) was performed using a Perkin Elmer DSC-7 machine fitted with an automatic sample changer. Approximately 2mg of each sample was accurately weighed into a 50 microlitre aluminium pan and crimp sealed with a perforated lid. The samples were heated at 20°C/minute over the range 40°C to 300°C

with a nitrogen gas purge. The thermal events are summarised in Table 6, and may be used to characterize the free base forms and mesylate salt.

Table 6

Thermal Events for Forms A, B, C, E and the mesylate salt

Form	Melting point (°C)
Form A	198
Form B	218
Form C	147
Form E	229
Mesylate	279

The water content of the hydrated form of the free base (Form D) at ambient conditions is commonly of the order of 9 to 10% (w/w). This is equivalent to 2.5 to 2.8 moles of water per mole of the free base. The water content at 90% RH was found to be 12.8% (w/w), this is equivalent to 3.6 moles of water, only 2 moles of which were found to represent bound water. The first mole was lost below 5% RH the second retained down to 1% RH see figure 11. It is likely that extended storage of the hydrated form below about 18% RH would result in dehydration. Furthermore, removal of the crystalline water results in the loss of the crystal lattice, the product being predominantly amorphous. This highlights a potential problem in using the conventional hydrated form in manufacturing a pharmaceutical formulation. Dehydration was observed on thermal analysis as a broad double endotherm at 97/113°C (See Figure 8)

The present invention is also illustrated by the following drawings in which:

Figure 1 shows the PXRD for the mesylate salt;

Figure 2 shows the DSC thermogram for the mesylate salt;

Figure 3 shows the PXRD for all the free base forms A, B, C, D and E;

Figure 4 shows the DSC thermogram for Form A;

Figure 5 shows the DSC thermogram for Form B;

Figure 6 shows the DSC thermogram for Form C;

Figure 7 shows the DSC thermogram for Form E;

Figure 8 shows the DSC thermogram for form D;

Figure 9 shows the moisture sorption of the mesylate salt;

Figure 10 shows the moisture sorption of Forms A, B and E; and

Figure 11 shows the moisture sorption of Form D.

The invention is illustrated by the Examples below, in which the following abbreviations may be used:

min	minute
NMR	nuclear magnetic resonance
h	hour

Example 1

Free Base Polymorphs of 4-Amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydro-2-isoquinolyl)-5-(2-pyridyl)quinazoline

(i) Form A

Under nitrogen, to a stirred suspension of 4-amino-2-chloro-6,7-dimethoxy-5-(2-pyridyl)quinazoline [see WO 98/30560, Example 12(a), 97g, 0.31mol] and *N*-(1,2,3,4-tetrahydro-5-isoquinolyl)methanesulfonamide hydrochloride [see WO 98/30560, Example 19(b), 89g, 0.34mol] in n-butanol (1.9l) was added triethylamine (161ml, 1.16mol). The reaction was warmed to reflux and stirred at reflux overnight. The reaction mixture was cooled to room temperature, concentrated *in vacuo* and the residue slurried in water (1.5l) and sodium hydrogen carbonate (15g) added. The resulting slurry was stirred over 3 nights, filtered, the solid washed with water (500ml) and dried overnight *in vacuo* at 50°C to give 158g of material.

The majority of the material (156g) was combined with a further portion of material (139g) prepared using a similar method and the combined solids were dissolved in

methanol (3l). The solution was filtered, concentrated *in vacuo* and the resulting solid dried overnight *in vacuo* at 50°C to give 287g of material.

The majority of the material (285g) was slurried overnight in acetone/water (4/1 by volume, 1.4l), filtered, the solid was washed with acetone/water 4/1 (300ml) and dried over 3 nights *in vacuo* at 50°C to give 251g of material.

The majority of the material was sieved through a 500μM sieve to afford the title compound (242g).

(ii) Form B

Under nitrogen, to a stirred suspension of 4-amino-2-chloro-6,7-dimethoxy-5-(2-pyridyl)quinazoline (166g, 0.53mol) and *N*-(1,2,3,4-tetrahydro-5-isoquinolyl)-methanesulfonamide hydrochloride (152g, 0.58mol) in n-butanol (2.0l) was added triethylamine (161ml, 1.16mol) and further n-butanol (1.3l). The reaction was warmed to reflux and stirred at this temperature for 11h. The reaction mixture was cooled to room temperature, concentrated *in vacuo* and the residue slurried in water (2.65l) and sodium hydrogen carbonate (28.5g) added. The resulting slurry was stirred overnight, filtered and the solid washed with water (500ml). The resulting damp solid was added to methanol (4 l) and the resulting suspension concentrated *in vacuo* until a thick suspension was obtained. Further methanol (150 ml) was added, and resulting slurry filtered and washed with methanol (3 x 50 ml). The resulting solid was dried over 3 nights *in vacuo* at 41°C. The dried solid was then slurried overnight in acetone/water (1/4 by volume, 1250ml), filtered, the solid washed with acetone/water 1/4 (3 x 50ml) and dried over 2 nights *in vacuo* at 54°C to afford the title compound (245g).

(iii) Form C

To a mixture of 4-amino-2-(5-methanesulfonamido-1,2,3,4-tetrahydro-2-isoquinolyl)-6,7-dimethoxy-5-(2-pyridyl)quinazoline (0.1g of a batch of approximately 90% purity, a Form D/amorphous mixture, 1.7mmol) and adipic acid (0.027g, 1.8mmol) was added acetone (1.25ml) and the resulting suspension stirred at room temperature over 3 nights.

The resulting suspension was filtered and dried overnight *in vacuo* at 48°C to afford a quantity of the title compound.

(iv) Form E

Under nitrogen, to a stirred suspension of 4-amino-2-chloro-6,7-dimethoxy-5-(2-pyridyl)quinazoline (105g, 0.33mol) in n-butanol (2.1l) was added *N*-(1,2,3,4-tetrahydro-5-isoquinolyl)methanesulfonamide hydrochloride (152g, 0.37mol) and triethylamine (106ml, 0.73mol). The reaction was warmed to reflux and stirred at reflux for 6h, cooled to room temperature and stirred overnight at room temperature. The mixture was then returned to reflux, stirred at reflux for 6h and cooled to room temperature and stirred at room temperature overnight. The reaction mixture was then concentrated *in vacuo* and the residue slurried in water (1.68l) and sodium hydrogen carbonate (17.9g) added. The resulting slurry was stirred overnight, filtered, and the damp solid was added to acetonitrile (1.16l). The resulting slurry was heated to reflux, then allowed to cool to room temperature and stirred at room temperature overnight. The resulting slurry was filtered and washed with acetonitrile (2 × 100ml). The damp solid was slurried in acetone/water (1/4 by volume, 800ml) overnight at room temperature, filtered, the solid washed with acetone/water 1/4 (2 x 50ml) and dried overnight *in vacuo* at 45°C to give 158g of material.

The majority of the material obtained from the above preparation (155g) was combined with further portions of material (596g) prepared in a similar manner and suspended in acetonitrile (5.28l). The suspension was warmed to reflux, stirred at reflux for 90 min, cooled to room temperature and stirred at room temperature overnight. The solid was collected by filtration, washed with acetonitrile (100 ml) and dried overnight *in vacuo* at 50°C to give the title compound (734g).

Example 2

4-Amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)- 5-(2-pyridyl)quinazoline mesylate

(i) The salt formation process described below was used to process Form B free base to the methanesulfonate salt.

Under nitrogen, a suspension of Form B 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline (2.0g) in butanone/water (10/1 by volume, 24ml) was heated to reflux over 20mins. Butanone/water 10/1 was added until a solution was achieved (an extra 3ml was added, bringing the total solvent volume to 27ml). The solution was left to cool to 50°C and methanesulfonic acid (0.38g, 4.0mmol) was added dropwise over 30 seconds. The addition vessel was washed with butanone/water 10/1 (2 × 0.25ml) and the washings were added to the reaction vessel. The resulting suspension was left to cool to room temperature and then stirred at this temperature for 2h. The solid was collected by filtration, washed with acetone (2 × 2ml), left to pull dry for 30min and dried overnight *in vacuo* at 54°C to afford the title compound (2.2g) as a white solid.

^{1}H-NMR (300 MHz, DMSO) δ : 2.30 (3H, s), 2.99 (3H, s), 3.04 (2H, m), 3.44 (3H, s), 3.93 (2H, m), 4.01 (3H, s), 4.91 (2H, s), 7.15 (1H, d), 7.28 (2H, m), 7.44 (1H, s), 7.57 (2H, m), 8.02 (1H, m), 8.77 (1H, m), 9.19 (1H, s).

(ii) The following preparation was used to process Form E free base to the methanesulfonate salt.

A suspension of Form E 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydro-2-isoquinolyl)-5-(2-pyridyl)quinazoline (1.0g, 1.97 mmol) in acetone/water (12/7 by volume, 9.5ml) was heated to reflux. Methanesulfonic acid (0.19g, 1.99 mmol) was added in one portion. The addition vessel was washed with water (1ml) and the resulting solution left to cool to room temperature overnight. The solid from the resulting suspension was collected by filtration and dried overnight *in vacuo* at 45°C to afford the title compound (1.14g) as a white solid.

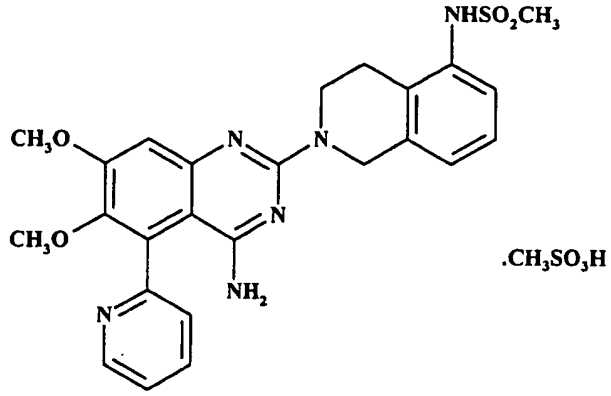
Example 3

***In vivo* activity**

The daily oral administration of 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline mesylate to male and female Sprague-Dawley rats at 30 mg/kg for 1 month induced changes linked to the pharmacological activity of the compound: however, there was no evidence of adverse effects.

Claims:

1. 4-Amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline mesylate of the formula



2. The mesylate salt as claimed in claim 1, characterised in that it exhibits an endothermic thermal event at about 279°C during differential scanning calorimetry.

3. The mesylate salt as claimed in claim 1 or claim 2, characterised by a powder X-ray diffraction pattern obtained by irradiation with copper K-alpha$_1$ X-rays of wavelength 1.5406Å, having the following main peaks:

Angle 2-Theta °	Intensity %
7.392	22.9
14.733	22.6
14.813	40.1
17.694	31
18.964	40.5
19.297	57.9
20.265	51
21.414	40
22.136	24
22.934	32.8
23.842	49.4
24.795	100
27.012	30.3
28.673	22.3
29.305	24.6

4. A substantially pure anhydrous crystalline free base form of 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline.

5. A free base form as claimed in claim 4, characterised in that it exhibits an endothermic thermal event at about 198°C during differential scanning calorimetry (designated Form A).

6. A free base form as claimed in claim 4 or claim 5, characterised by a powder X-ray diffraction pattern obtained by irradiation with copper K-alpha$_1$ X-rays of wavelength 1.5406Å, having the following main peaks:

Angle 2-Theta °	Intensity %
6.002	21.1
8.893	22.9
9.401	25.1
11.105	33.4
12.000	100.0
12.071	50.2
13.060	25.1
17.040	30.0
17.888	33.4
18.872	51.9
21.925	57.5
22.346	94.6
22.821	22.7
23.282	40.8
23.494	37.3
23.884	92.4
24.298	42.7
25.674	30.1
27.641	24.4
30.282	25.8
35.158	21.2
43.943	20.5

7. A free base form as claimed in claim 4, characterised in that it exhibits an endothermic thermal event at about 218°C during differential scanning calorimetry (designated Form B).

8. A free base form as claimed in claim 4 or claim 7, characterised by a powder X-ray diffraction pattern obtained by irradiation with copper K-alpha$_1$ X-rays of wavelength 1.5406Å, having the following main peaks:

Angle 2-Theta °	Intensity %
9.004	37.5
9.725	41.2
10.526	40.7
13.493	30.2
13.897	74.4
15.569	25.2
15.883	48.3
17.122	30.0
18.727	62.9
20.407	62.2
20.919	31.2

22.551	72.7
22.769	20.2
23.418	100.0
23.904	24.9
23.997	24.5
25.049	21.4
25.209	32.4
26.512	36.5
26.758	30.5
26.918	20.7
26.989	25.4

9. A free base form as claimed in claim 4, characterised in that it exhibits an endothermic thermal event at about 147°C during differential scanning calorimetry (designated Form C).

10. A free base form as claimed in claim 4 or claim 9, characterised by a powder X-ray diffraction pattern obtained by irradiation with copper K-alpha$_1$ X-rays of wavelength 1.5406Å, having the following main peaks:

Angle 2-Theta°	Intensity %
7.860	63.2
12.133	24.3
13.690	37.3
15.008	35.4
15.794	32.6
16.274	27.9
17.488	24.7
18.601	76.6
18.964	32.9
19.727	51.4
20.121	29.0
21.730	100.0
22.310	39.0
22.830	72.0
23.102	27.7
23.598	75.9
23.884	24.7
24.479	50.5
24.777	21.2
25.093	59.3
25.257	52.6
26.283	22.0
26.634	28.5
27.309	20.8
27.574	28.7
29.792	30.7
31.590	22.4
31.939	28.9
38.576	20.2
39.190	23.3

11. A free base form as claimed in claim 4, characterised in that it exhibits an endothermic thermal event at about 229°C (designated Form E).

12. A free base form as claimed in claim 4 or claim 11, characterised by a powder X-ray diffraction pattern obtained by irradiation with copper K-alpha$_1$ X-rays of wavelength 1.5406Å, having the following main peaks:

Angle 2-Theta °	Intensity %
9.675	23.0
16.914	30.8
19.315	38.5
19.358	42.2
19.444	31.1
19.778	26.6
23.852	100.0
25.280	28.2
32.760	25.6

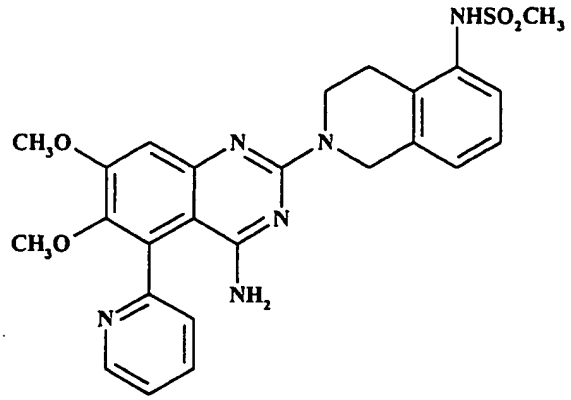
13. A pharmaceutical formulation containing 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline in the form of the anhydrous free base or the mesylate salt, as defined in any one of claims 1 to 12, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

14. 4-Amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline in the form of the anhydrous free base or the mesylate salt, as defined in any one of claims 1 to 12, for use as a pharmaceutical.

15. The use of 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline in the form of the anhydrous free base or the mesylate salt, as defined in any one of claims 1 to 12, in the manufacture of a medicament for the treatment of benign prostatic hyperplasia.

16. A method of treatment of benign prostatic hyperplasia, which comprises administering a therapeutically effective amount of 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline in the form of the anhydrous free base or the mesylate salt, as defined in any one of claims 1 to 12, to a patient suffering from such a disorder.

17. A process for the preparation of 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl) quinazoline mesylate, as defined in claim 1, which comprises the addition of methanesulphonic acid to a suspension or solution of 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline of the formula



in a suitable solvent, and collection of the precipitated solid.

18. A process as claimed in claim 17, wherein the solution of 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)-quinazoline is maintained at a temperature above room temperature before the addition of the methanesulphonic acid.

19. A process as claimed in claim 17 or claim 18, wherein the solvent used is a mixture of butanone and water.

20. A process as claimed in any one of claims 17, 18 and 19, wherein the solvent is a 10:1 by volume mixture of butanone and water.

21. A process as claimed in claim 19 or claim 20, comprising the steps of:

(a) heating a suspension of 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline in butanone/water to reflux;

(b) adding butanone/water until a solution is achieved;

(c) cooling the solution;

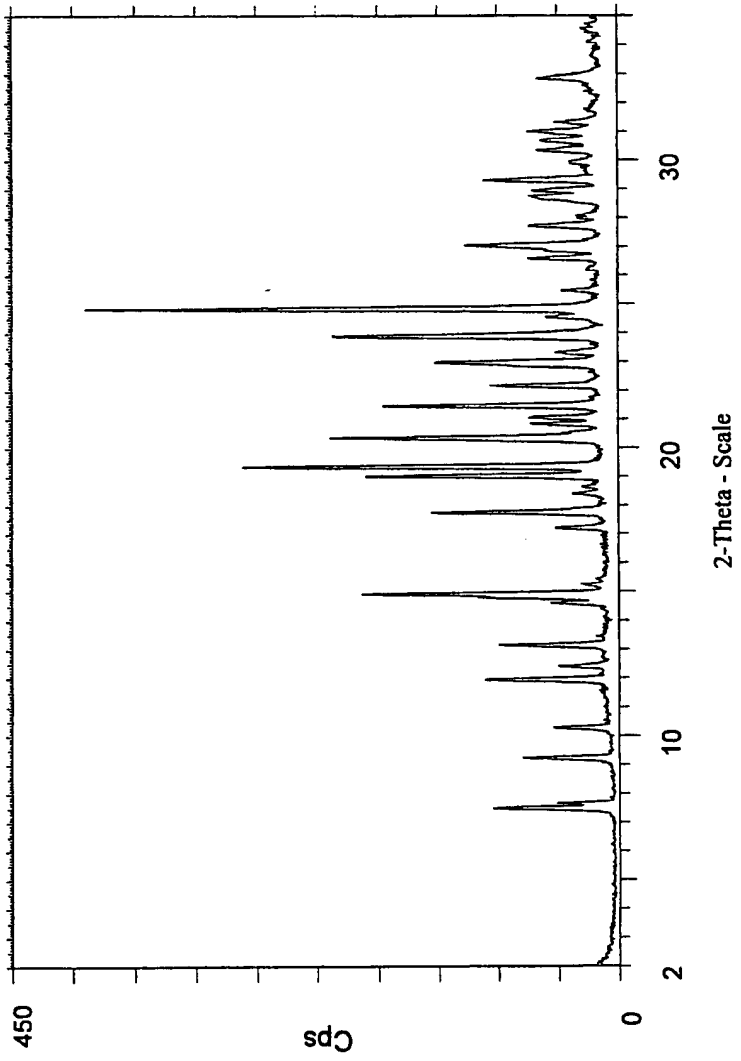
(d) adding methanesulfonic acid; and

(e) collecting the resulting solid by filtration.

22. A process as claimed in any one of claims 17 to 21, wherein the 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline is present as Form E, as defined in claim 11 or claim 12.

Figure 1

PXRD Pattern for the Mesylate Salt



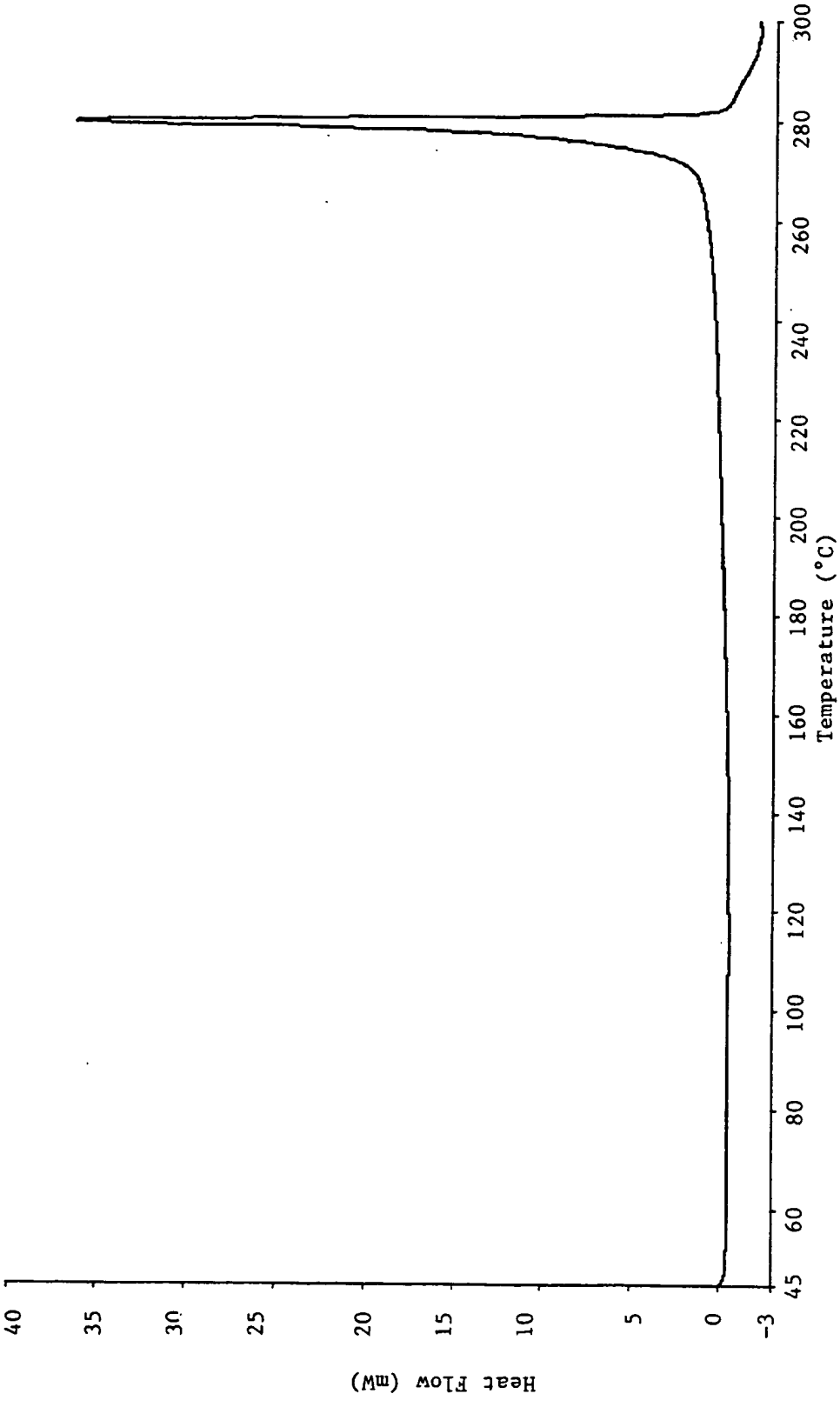


Figure 2
DSC Thermogram for The Mesylate Salt

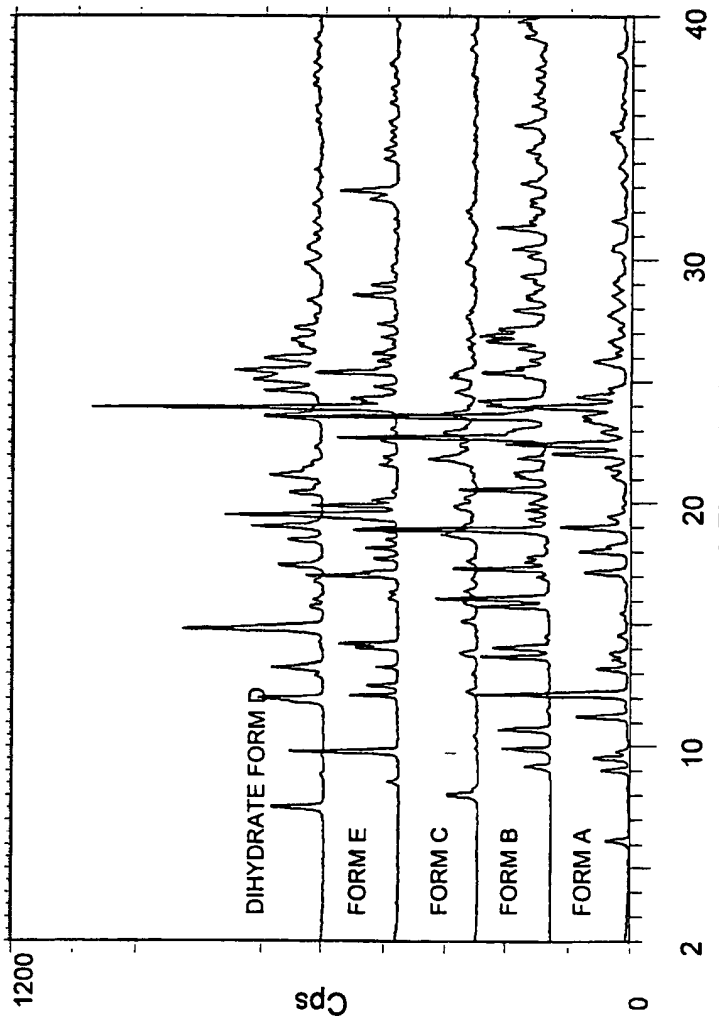


Figure 3
PXRD Patterns for All The Free Base Forms

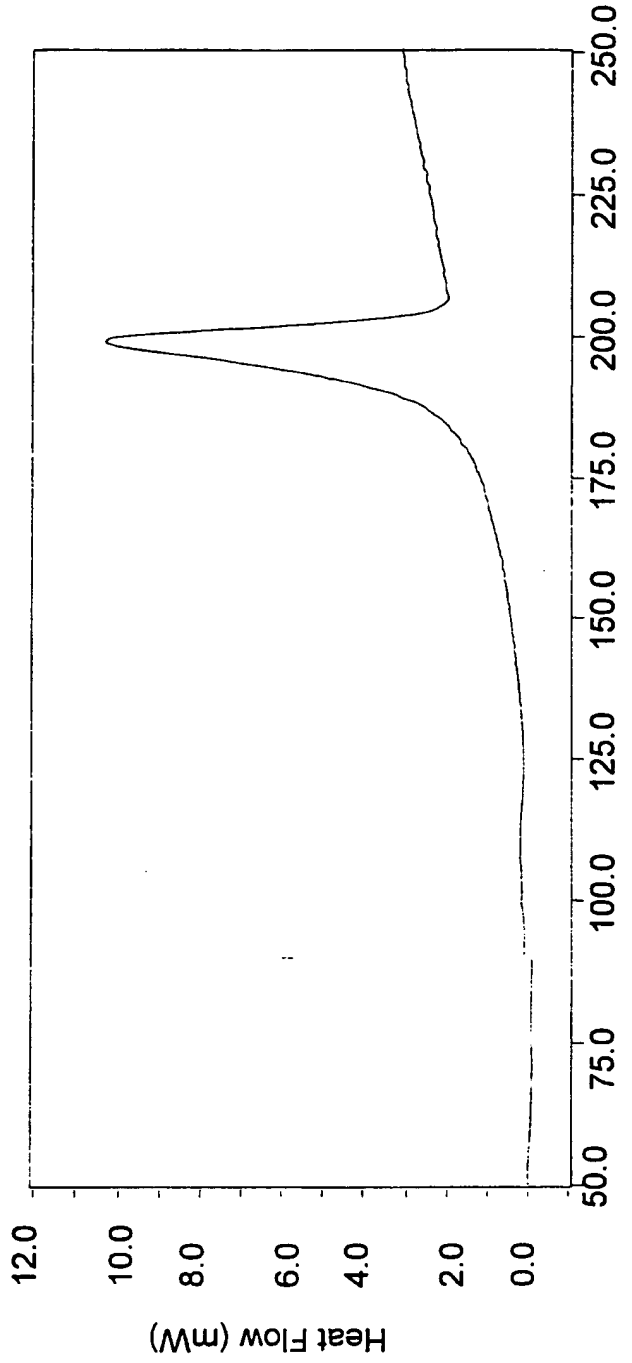


Figure 4

DSC Thermogram for The Free Base Form A

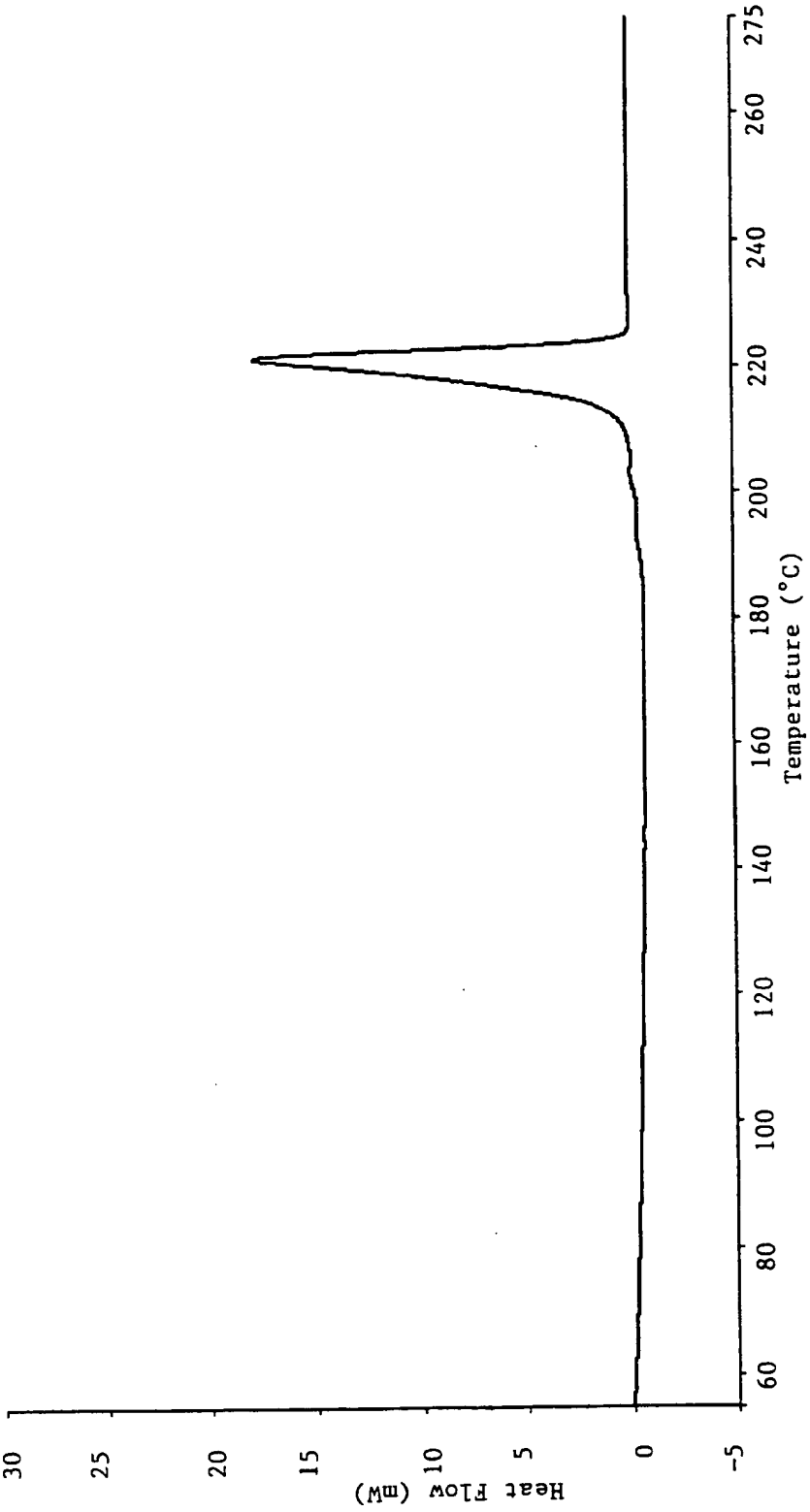


Figure 5
DSC Thermogram for The Free Base Form B

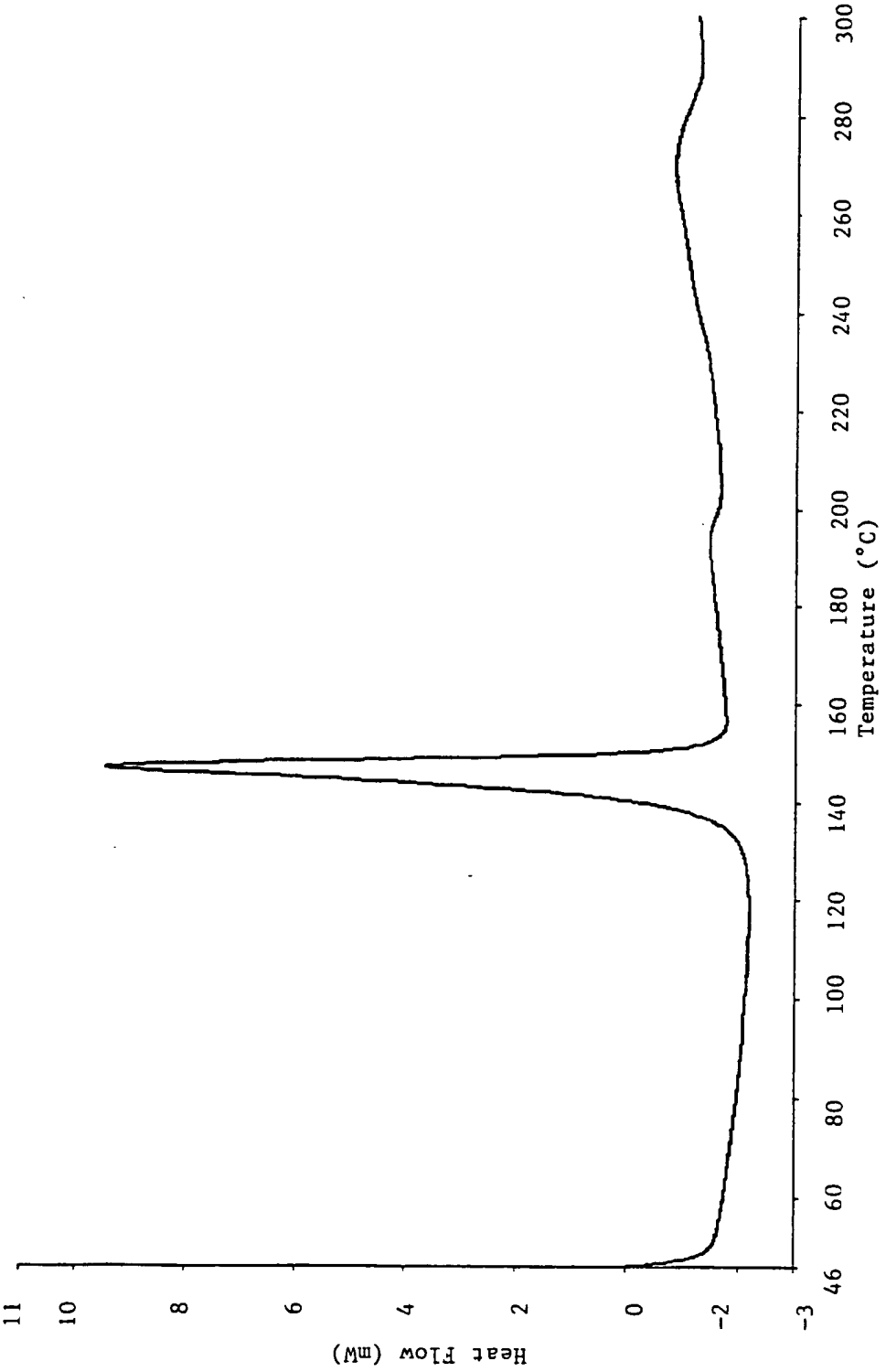


Figure 6
DSC Thermogram for The Free Base Form C

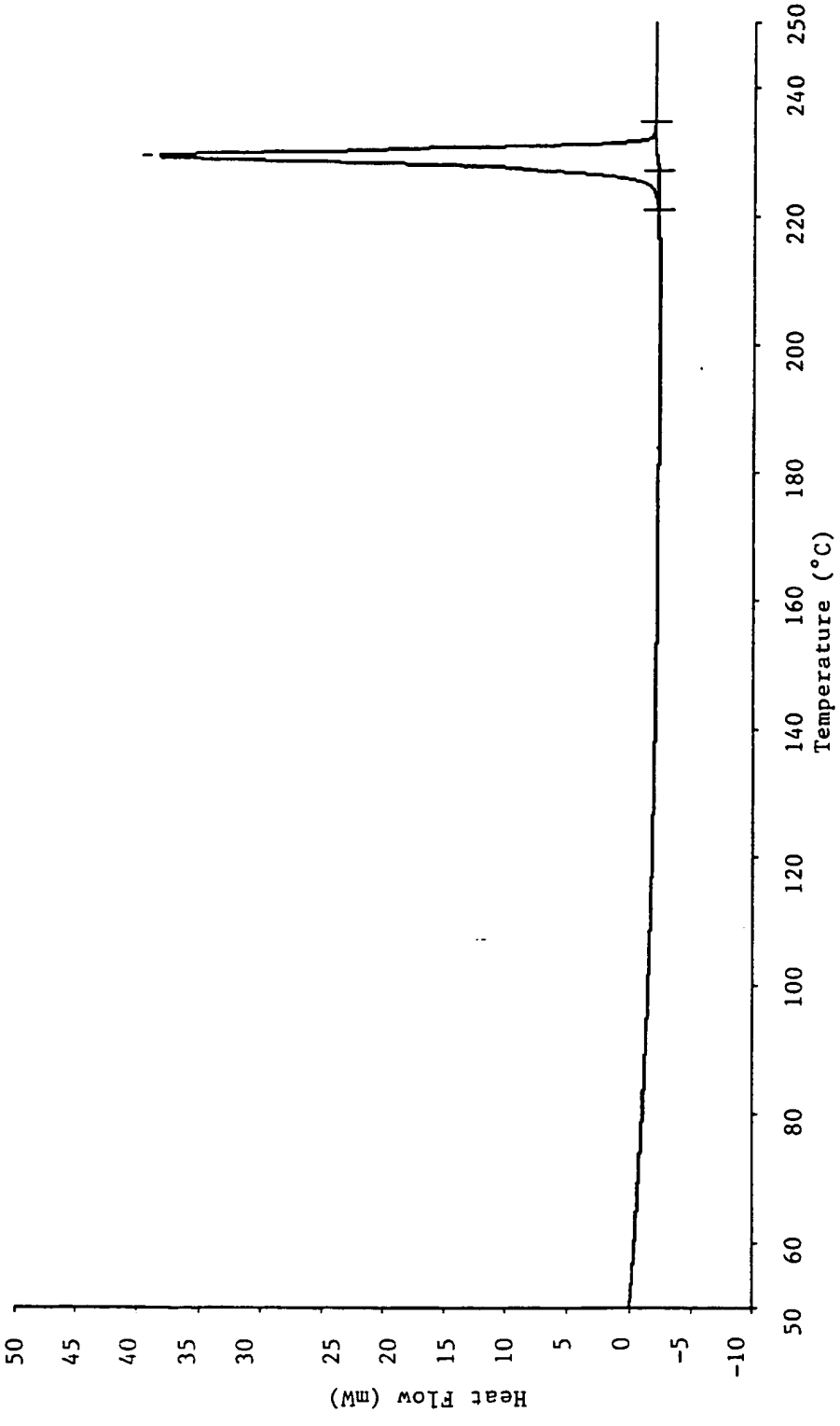


Figure 7
DSC Thermogram for The Free Base Form E

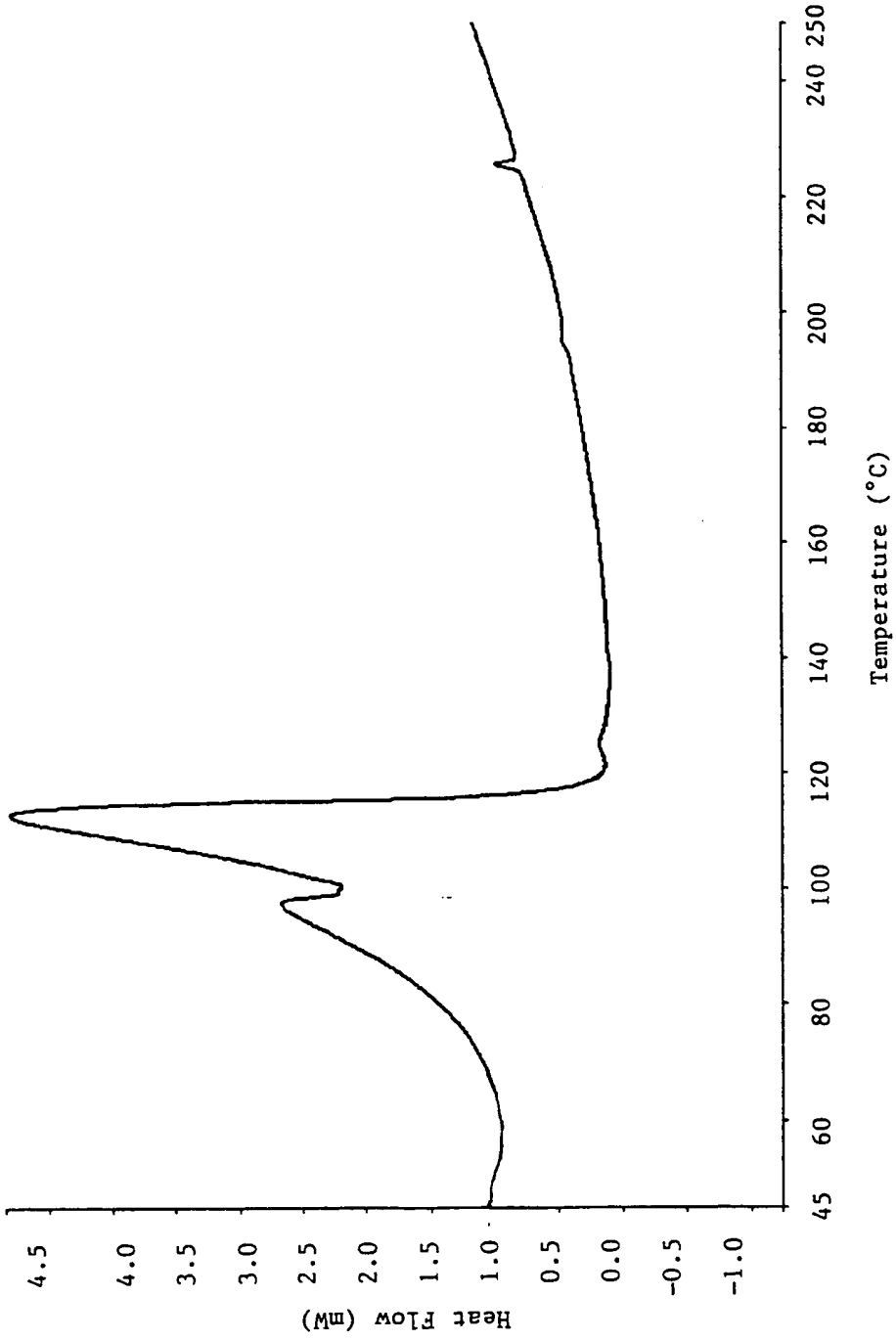


Figure 8
DSC Thermogram for The Free Base Dihydrate, Form D

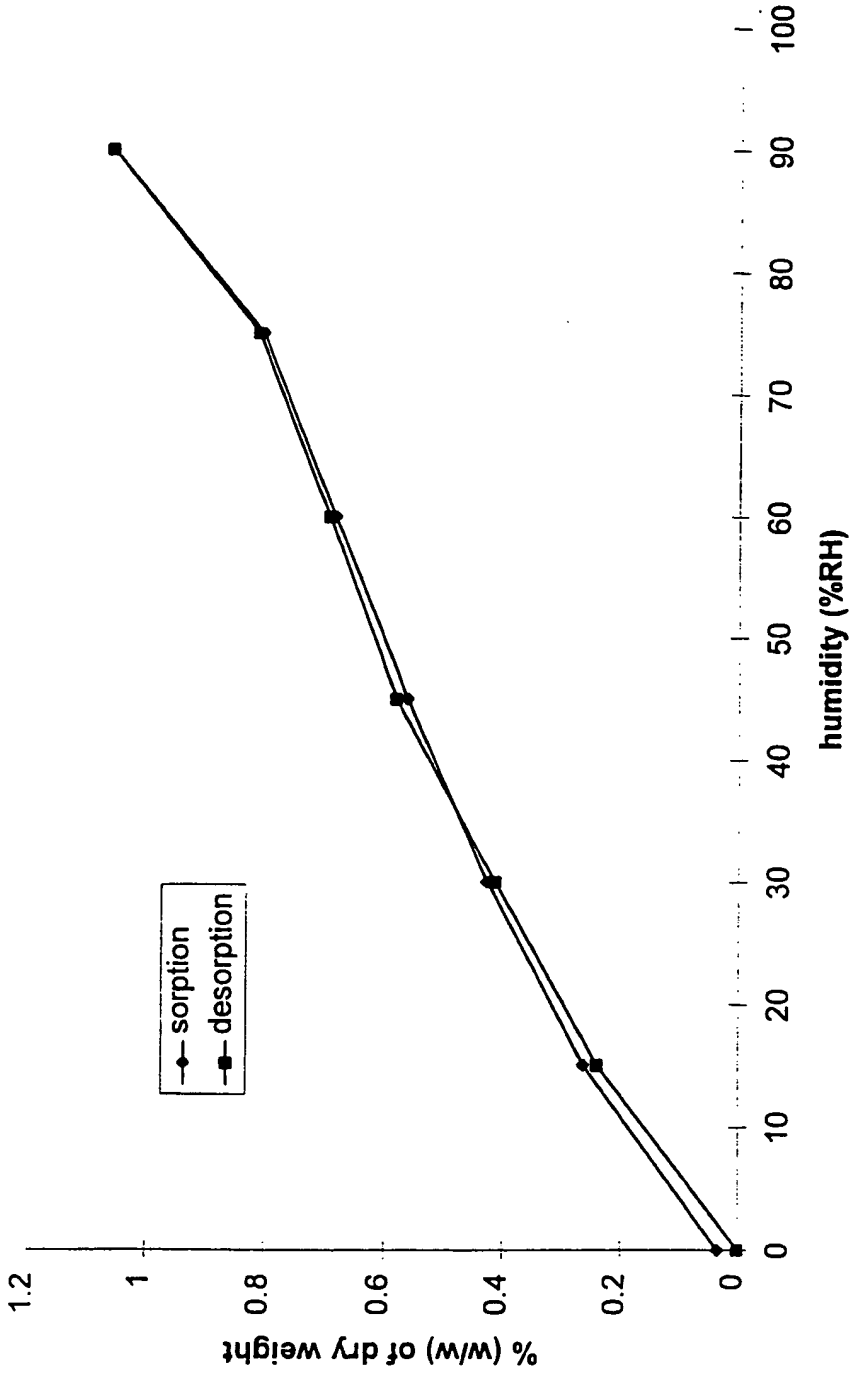


Figure 9
Moisture Sorption of The Mesylate Salt at 30°C

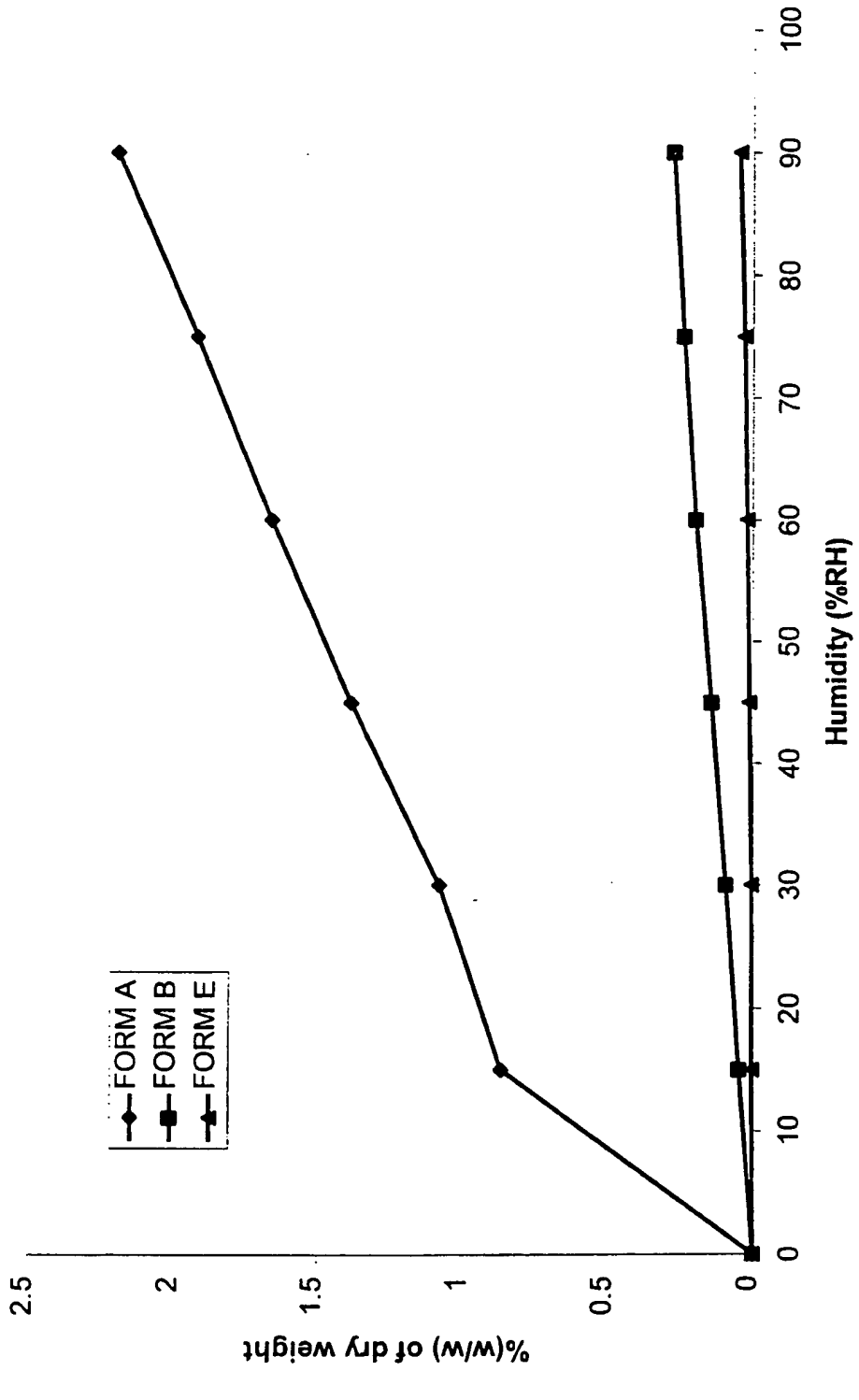


Figure 10
Moisture Sorption Isotherm for The Forms A, B and E

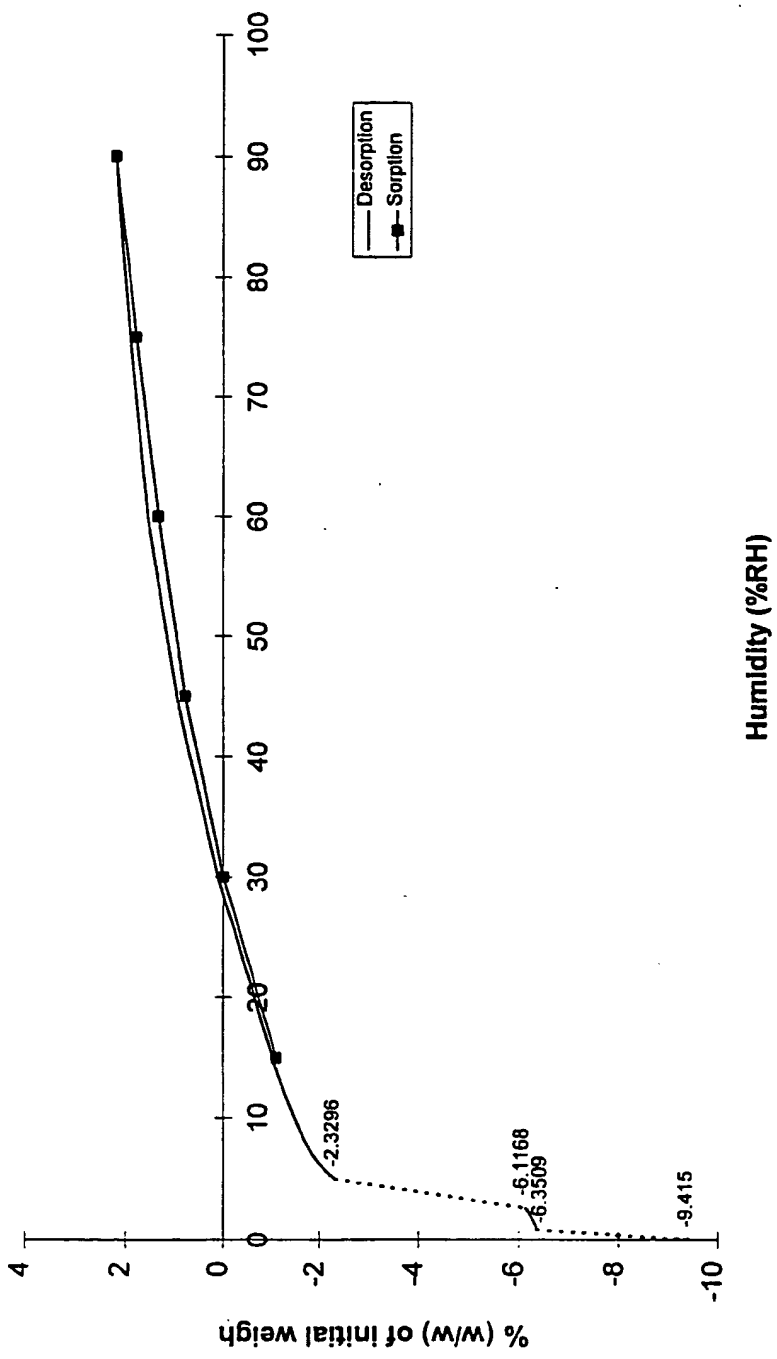


Figure 11
Moisture Sorption of The Free Base Form D (Di-Hydrate) at 30°C

INTERNATIONAL SEARCH REPORT

Inte 'onal Application No
PCT/IB 01/00244

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/14 A61K31/505 A61P13/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, BEILSTEIN Data, WPI Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 30560 A (PFIZER LTD., UK;PFIZER INC.; FOX, DAVID NATHAN ABRAHAM) 16 July 1998 (1998-07-16) cited in the application page 36, line 12 -page 37, line 13; example 19	1-22
A	WO 88 01998 A (MERCK PATENT GMBH) 24 March 1988 (1988-03-24) page 1, line 5 -page 1, line 16	1-3, 13-22

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
14 May 2001	25/05/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seelmann, I

INTERNATIONAL SEARCH REPORT

.formation on patent family members

Inte ional Application No
PCT/IB 01/00244

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